REMARKS

Claim 4 is pending in the instant application. Claim 4 has been rejected. Claim 4 has been amended. Reconsideration is respectfully requested in light of the amendments and the following remarks.

I. Objection to Claim 4

Claim 4 has been objected to because of informalities, namely misspelling of the word "picogram" in step (d) of the claim. Applicant has corrected the spelling errors and withdrawal of this rejection is respectfully requested.

II. Rejection of Claim 4 Under 35 U.S.C. 112, First Paragraph

Claim 4 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner suggests that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claim invention. The Examiner suggests that the recitation of the limitation "as small as 9

picograms per milliliter of blood" lacks adequate description and support in the specification as filed. Claim 4 has also been rejected under 35 U.S.C., 112, first paragraph, as failing to comply with the written description requirement for recitation of the term "natriuretic peptide" since the specification as filed only contains teaching of monitoring levels of brain natriuretic peptide (BNP) or N-terminal probrain natriuretic peptide (NTproBNP), not any and all other natriuretic peptides that exist. Finally, claim 4 has been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for BNP and NTproBNP, does not reasonably provide enablement for any and all natriuretic peptides as broadly claimed. As a result, the Examiner suggests that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claim. The Examiner cites relevant art relating to, for example, atrial natriuretic peptide, pro-atrial natriuretic peptide, and C-natriuretic peptide to support this position, where the art teaches that such peptides would not be useful as markers of ischemic cardiovascular disease in the instant method

of claim 4. Applicants respectfully traverse these rejections under 35 U.S.C. 112, first paragraph.

At the outset, in an earnest effort to advance the prosecution and facilitate allowance of the claim, Applicants have amended claim 4 to recite that the method of the present invention relates to monitoring levels of either BNP or NTproBNP in patients. Further, the claim was amended to recite that the method of the present invention involves the active steps of (e) determining an absolute level of change in the actual pg/ml of blood level of BNP or NTproBNP, as well as (f) diagnosing cardiac ischemia in an individual by identifying the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being greater than 5 pg/ml of NTproBNP. Support for these amendments to the claim can be found throughout the specification as filed but in particular at pages 6-11 where results of a clinical study are described discussing measurement of blood levels of both BNP and NTproBNP, and that changes in the levels of these peptides after application of an exercise stress test in a patient were predictive of cardiac ischemia. Specific support for recitation of the absolute blood level changes as being greater than 10

pg/ml of BNP or greater than 5 pg/ml of NTproBNP can be found at Table 6. Accordingly, the claims as amended meet the requirements of 35 U.S.C. 112, first paragraph, with respect to both the written description requirement and the enablement requirement. Withdrawal of these rejections is respectfully requested.

III. Rejection of Claim 4 Under 35 U.S.C. 112, Second Paragraph

Claim 4 has been rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that the claim recites "the actual picogram per milliliter of blood" in step (d) and this limitation lacks sufficient antecedent basis. The Examiner also suggests that the recitation of "the first blood sample of as small as 9 picograms per milliliter of blood" is vague. Applicants have amended claim 4 to remove the language identified by the Examiner. Accordingly, the claim as amended meets the requirements of 35 U.S.C. 112, second paragraph, and withdrawal of this rejection is respectfully requested.

IV. Rejection of Claim 4 Under 35 U.S.C. 102(e)

Claim 4 has been rejected under 35 U.S.C. 102(e) as being anticipated by Zoghbi et al. (US Patent Application 2004/0243010). The Examiner suggests that this reference discloses a method of determining the level of BNP in a plasma sample from a patient prior to exercise to establishing a baseline, and also determining the level of BNP in a sample from the patient post exercise, as well as teaching that the exercise stress test can be performed with myocardial perfusion imaging wherein the dual isotope, rest-stress protocol is used. The Examiner further suggests that the clause starting with "wherein" in the claims does not limit the invention as it does not recite any additional active steps. The Examiner also suggests that Applicants statements regarding this patent application in the previous reply (dated October 10, 2008) were "not on point" because the sections pointed to in the reply by Applicants related to comparison of non-ischemic versus ischemic groups and not to comparison of baseline and post-exercise levels of BNP in a single patient, as claimed in instant claim 4. Applicants respectfully traverse this rejection.

As discussed *supra*, in order to advance the prosecution and facilitate allowance of the claim, Applicants have amended claim 4 to more clearly define the method of the present invention. Claim 4 as amended recites a method for detecting cardiac ischemia in an individual suspected of suffering from ischemic cardiovascular disease that comprises measuring actual picrogram per milliliter of blood levels of either BNP or NTproBNP in blood samples from an individual both before and after the individual has completed an exercise stress test with myocardial perfusion imaging wherein a dual isotope, rest-stress protocol is used, and then the active steps of determining an absolute level of change in the actual pg/ml of blood level of BNP or NTproBNP, as well as diagnosing cardiac ischemia by identifying the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being greater than 5 pg/ml of NTproBNP. Support for these amendments to the claim can be found throughout the specification as filed but in particular at pages 6-11 where results of a clinical study are described and levels of both BNP and NTproBNP were measured and changes in the levels of these peptides after application of an exercise stress test in a patient were

predictive of ischemia. Specific support for recitation of the absolute blood level changes as being greater than 10 pg/ml for BNP or greater than 5 pg/ml for NTproBNP can be found at Table 6. Applicants point out that data are provided showing that the method of the present invention is based on measurement of actual picrogram per milliliter of blood levels and that the changes in the blood levels after exercise relate to either the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being greater than 5 pg/ml of NTproBNP. Moreover, in Table 6, the data gathered using the method of the present invention are shown to be both sensitive and specific with a high level of diagnostic accuracy as compared in particular to ECG changes, with a BNP change of equal to 10 pg/ml being useful for diagnosis.

Zoghbi et al. (US2004/0243010) disclose use of an entirely different endpoint for assessing risk of ischemia in patients, including the method involving measurement of blood levels of BNP in the same patient both before and after exercise. As taught in Example 5, Table 1, page 9 of the application, although BNP increased from baseline to immediately post-

exercise in individuals with ischemia as well as those without ischemia, the actual pg/ml change in BNP levels post exercise in patients either with or without ischemia had a median value of 15.5 pg/ml in ischemia patients, i.e., patients diagnosed with ischemia, and that the difference between the change in pg/ml of BNP between ischemic patients and those identified as being not ischemic was not statistically significant (p-value reported to be 0.115). Therefore, absolute levels of BNP in blood did not differ between such individuals (see paragraphs [0104] and [0105]). As stated in the previous reply (dated October 10, 2008), the application states *"Neither the absolute BNP levels at peak nor the absolute level of rise from baseline to immediate post-exercise differentiated between ischemic and non-ischemic patients."* [see paragraph [0104]). Contrary to the Examiner's suggestion, this teaching is on point. This is because nowhere does this application teach or suggest the actual magnitude of changes in blood levels of BNP in any individual patients after exercise as compared to before exercise (*i.e.,* individual patient data are not provided). The patent application instead teaches that what is important is the "percent increase in BNP" for any one individual or for any

population. This teaching by Zoghbi et al. is not the same as the method of claim 4 as amended which recites specifically identifying the actual increases in BNP or NTproBNP blood levels, in pg/ml and that this identification is diagnostic of cardiac ischemia. As a result, the application of Zoghbi teaches away from the method of the present invention which relies on measurement of actual levels of natriuretic peptides in blood, not percent increases as is used by Zoghbi et al. MPEP 2131 states that in order to anticipate an invention the cited reference must teach each and every limitation of the claims. As discussed *supra*, the cited reference fails to diagnose cardiac ischemia based on the use of actual picrogram levels of BNP or NTproBNP in blood. Accordingly, the reference fails to teach or suggest the limitations of the claims as amended and withdrawal of this rejection is respectfully requested.

V. Rejection of Claim 4 Under 35 U.S.C. 103(a)

Claim 4 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Valkirs et al. (US Patent Application 2003/0109420; hereafter referred to as the '420 application), in view Zoghbi et al. (US2004/0243010), and further in view of

DeVito (U.S. Patent No. 5,249,124, hereafter referred to as the '124 patent). The Examiner suggests that the '420 application discloses a method of diagnosing myocardial ischemia in a patient by determining a level of BNP in a sample isolated from the patient, including before and after a stress test, and that if the test sample is greater than the control sample, then the diagnosis of myocardial ischemia is made. The Examiner suggests that it would have been obvious for one of ordinary skill in the art to incorporate a stress test with myocardial perfusion studies as taught by the '124 patent into the method of the '420 application because the '420 application teaches a generic method with respect to a stress test and the '124 patent teaches that such studies provide two images of the heart and the relationship between those images shows heart muscle affected by arteriosclerosis and where it is infarcted. The Examiner suggests it would have been obvious as well to one of ordinary skill to incorporate immunoassays as taught by Zoghbi et al. for determining the level of BNP in the method of the '420 application because this application teaches that immunoassay can be used for determining BNP levels. The Examiner further suggests that the clause starting with "wherein" in the claims

does not limit the invention as it does not recite any additional active steps. Applicants respectfully traverse this rejection.

As discussed *supra*, Applicants have amended claim 4 to more clearly define the method of the present invention. Claim 4 as amended recites a method for detecting cardiac ischemia in an individual suspected of suffering from ischemic cardiovascular disease that comprises measuring actual picogram per milliliter of blood levels of either BNP or NTproBNP in blood samples from an individual both before and after the individual has completed an exercise stress test with myocardial perfusion imaging wherein a dual isotope, rest-stress protocol is used, and then the active steps of determining an absolute level of change in the actual pg/ml of blood level of BNP or NTproBNP, as well as diagnosing cardiac ischemia by identifying the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being greater than 5 pg/ml of NTproBNP. Support for these amendments to the claim can be found throughout the specification as filed but in particular at pages 6-11 where results of a clinical study are described where levels of both BNP and NTproBNP are measured and changes in the

levels of these peptides after application of an exercise stress test in a patient were predictive of ischemia. Specific support for recitation of the absolute blood level changes as being greater than 10 pg/ml for BNP or greater than 5 pg/ml for NTproBNP can be found at Table 6.

The '420 application discloses measuring levels of BNP in patients as a way of diagnosing myocardial ischemia in the patient. Review of the specific teaching in the application, however, reveals a key difference between the teachings of the '420 application and claim 4 as amended. The method of the '420 application depends on the measurement of absolute thresholds for BNP in blood, both in populations and in individuals. As is taught at pages 31-32, baseline levels of BNP correlate with past medical history, where "higher quartile BNP levels" were associated with cardiovascular diseases that included congestive heart failure, renal function, and ECG changes. Then at pages 39 and 40, the '420 patent application teaches in various claims that the "threshold BNP level is at least" values such as 60 pg/ml or 80 pg/ml. Nowhere does this patent application teach or suggest that an increase in a baseline level of BNP in a patient following a stress test of any type of only 5 pg/ml, in

the case of NTproBNP, or 10 pg/ml, in the case of BNP, would be useful for diagnosis of cardiac ischemia in a patient. Therefore, this patent application fails to teach or suggest the method of claim 4 as amended where diagnosis of cardiac ischemia relies on identifying specific pg/ml increases in either BNP or NTproBNP.

As discussed *supra*, Zoghbi et al. also fails to teach or suggest that an increase in a baseline level of BNP in a patient following a stress test of any type of only 5 pg/ml, in the case of NTproBNP, or 10 pg/ml, in the case of BNP, would be useful for diagnosis of cardiac ischemia in a patient. Moreover, the '124 patent discloses only the use of multi-isotope imaging for myocardial perfusion studies.

MPEP 2143 states that in order to establish a *prima facie* case of obviousness the references cited and combined must teach the limitations of the claims. As discussed *supra*, the cited references fail to teach the limitations of the claim as amended which recites diagnosing cardiac ischemia by identifying actual blood level changes in BNP of greater than 10 pg/ml or NTproBNP blood level changes of greater than 5 pg/ml, when levels are measured in the patient both before and after an exercise stress

test with myocardial perfusion imaging where a dual isotope, rest-stress protocol is used. Accordingly, the references, either when combined or alone fail to teach or suggest the limitations of the claim as amended and withdrawal of this rejection is respectfully requested.

VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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